EXPLANATION OF FURTHER AMENDMENT

Typographical errors have been found in the specification and amended claims. Though the most preferred NA value range at the time of filing the application of 0.4 and 0.55 is given correctly in the specification at page 2 line 32 (albeit, with an extraneous decimal point following the first "5"), and correctly in the detailed specification at page 12, lines 14 and 15 and in the Abstract, at other places the numerical values are incorrectly given with a decimal point that does not precede the integers 4 and 5.

These errors in the specification are hereby corrected.

Also, by the present amendment, the previous wordings of claims 1 and 3 with respect to NA values are restored and new claims 52 has been added. Claims 53 to 56 have also been added to cover further important features.

The previous Remarks provided in the earlier amendment of November 17, 2008, are Restated as follows to correspond with the present amendment.

RESTATED REMARKS

In response to the Office Communication of October 15, 2008, Applicants withdraw the stated election of Group II claims contained in its response of September 22, 2008, and now elect Group I without traverse and provide below their response to the Examiner's rejection of the Group I claims. Applicants reserve the right to pursue the non-elected claims separately.

As will be seen from the preceding Amendment and this Further Amendment, the elected claims have been amended to meet the issues raised under Section 112 in the office action dated 3/31/08. Claims 10 and 14-19 have been cancelled without prejudice. Without prejudice, the method claims have been amended to require use of the reader of claim 1, and therefore are submitted to fall within elected Group I and to be appropriate for examination here. New claims 51-56 have been added.

The following remarks address the claim rejections that are based on Section 103 of the office action of 3/31/08.

Claims 1, 8, 21, 24 and 26

As described in the Background Section of the present application, it has been predicted that micro-array technology would ultimately develop to enable practical use in the clinic, e.g. for clinical investigations and clinical diagnosis, but that prospect has seemed far off. Among reasons for this has been the very high cost of the required equipment. In particular, the reader of fluorescent micro-arrays is a critical component for such use of the arrays. The present invention represents a solution to the need for low cost readers for clinical work.

The invention of **claim 1,** now amended to more clearly bring out these aspects which are submitted to have been inherent in the original claim, is a reader that can be <u>inexpensive yet clinically accurate</u> to read a two dimensional planar array of features that carry photo-responsive markers. The reader, while <u>requiring no scanning mechanism,</u> comprises the combination of a light source in the form of at least one <u>light-emitting diode</u> <u>that floods entirely</u> the array of features at an angle between about 20 to 50 degrees to the planar extent of the substrate to excite the photo-responsive markers, and an image collection and recording system that employs a two dimensional sensor in the form of a solid-state array of photosensitive elements; the image collection and recording system, acting on an image-acquiring axis substantially normal to the extent of the substrate, is constructed and arranged to <u>apply to the photosensitive array, in a single frame, an image of the entire array of features, the image applied to the photosensitive array being of size</u> the <u>same order of magnitude</u> as the size of the array of features, the image size defined as being within a range <u>between magnification of up to about 25% and reduction down to 75%,</u> employing an intermediate numerical aperture, enabling recording the image with clinical accuracy in a simple and hence low cost construction.

Claim 1

Claim 1 was rejected as being unpatentable over Rava et al (5,545,531) in view of Trulson et al (5,578,832). However, upon review, it is clear that neither of these references,

alone nor in any proper combination, suggests the low cost and effective reader construction of claim 1.

(1) Each of these cited references requires scanning to assemble an image of the entire array. This requires a costly mechanism for moving the array relative to the recording system. (2) Neither teaches a diode lighting system that floods entirely the array with excitation radiation. (3) Neither teaches creating an entire image on the sensor array of the same order of magnitude as the size of the array of photo responsive features to enable imaging in a single frame. (4) Neither teaches the use of the numerical aperture employed.

It is submitted that it would require impermissible hindsight reconstruction in the extreme to say that these references fairly teach the claimed reader.

In respect of Rava, Fig. 1 illustrates a stage translation device 140. In the embodiment described by Rava in detail, confocal detection is employed, and the location to which a small light spot is directed is controlled, for example, by an x-y-z translation table, col. 5, lines 25-29. In respect of Fig. 2 we draw attention in Rava that "Fig. 2 depicts the scanning of a biological chip plate", col. 2, lines 6 and 7. Note that the image at any instant is a line, not that of a two dimensional array. No disclosure is found in Rava of creating an entire image of a two-dimensional array of features in a single frame on the sensor array of the same order of magnitude as the size of the array of photo responsive features and avoiding use of scanning, nor the other features, including use of diode lighting to entirely flood the array with excitation illumination, that complete the low cost system.

Trulson does not make up for the deficiencies of Rava in features or goal. (1) Trulson mentions a light emitting diode within a catalogue of 9 different lighting techniques (col. 6, lines 15-21). This certainly can not be said to identify diodes as a key component for flooding the entire array for achieving the non-scanned, single image frame, low cost reader of claim 1. (2) In Trulson, an image is to be significantly magnified (2X, col. 8, line 8, or 5X, col. 8, line 21). (3) In Trulson, only a line across an array is imaged in any one frame; scanning is to be employed to construct an entire image, see col. 8 lines 31-38 and 46-54).

We do note Trulsons' statement beginning at column 27, line 7 that "In addition, resolution of the image may be manipulated by increasing or decreasing the magnification of the collection optics". This truism is certainly no direction to a person of ordinary skill to seek to

build a simple, non-scanned reader and for achieving that purpose, to limit magnification to a very small amount or eliminate it entirely and decrease the image size, i.e. limit to the range between magnification of only about 25% down to reduction of the image 75%.

It is submitted that claim 1 is not obvious and is patentable over Rava in view of Trulson.

Claim 8

In respect of claim 8, also rejected on Rava in view of Trulson, there is no disclosure in these references of the array reader of present claim 1 in which the field of view of the array reader has a diameter of 10 mm or more. Rava and Trulson are concerned with confocal imaging in which a spot of only 2 micron is illuminated, or with line imaging in which as many as 6 different lines are successively imaged to cover one row of tiny features, see Rava column 5 lines 17 and 67 and column 6, line 27 and see Tulson, col. 8 lines 31-38.

Claim 21

Claim 21, also rejected on Rava in view of Trulson, calls for the array reader of claim 1 in combination with a substrate carrying excitation energy reference features distributed across the two-dimensional array of features, the image collection and recording system including a normalizing arrangement for normalizing data detected in the vicinity of respective reference features based on the quantity of detected emission from the respective reference features. The Examiner cites no portion of Rava or Trulson to justify the rejection of claim 21 on those references.

Claim 24

Claim 24, also rejected on Rava in view of Trulson, calls for the array reader of claim 1 in which the illuminating system includes light source diodes selected respectively to excite Cy3 and Cy5, and the image collection and recording system includes changeable band-pass filters suitable to permit passage of emissions respectively from Cy3 and Cy5 or a single band-pass filter is provided suitable to permit multiple band-pass emissions of Cy3 and Cy5. As the Examiner has admitted, Rava shows no diode illumination. The fact that the well known dyes Cy3 and Cy5 are mentioned in Rava, certainly does not make the claimed combination obvious.

Claim 26

Claim 26, also rejected on Rava in view of Trulson, calls for the array reader of claim 1 in which the illumination system that illuminates the entire two dimensional array includes a diode light source followed by a homogenizer effective to reduce variation in flux density across the two dimensional field of illumination. Applicants of course admit that homogenizers used with diodes are well known per se, but that does not detract from the novelty and patentability of the combination of claims 1 and 26, for the reasons previously discussed and the fact that here the homogenizer is effective to reduce variation in flux density across the entire two dimensional field of illuminated array that is imaged in one frame on the sensor array. As the Examiner recognizes, Rava does not disclose that the illumination system includes a homogenizer. Trulson does refer to homogenizing, but in a very different context. Trulson's Figure 21 relates to a linear (not two dimensional) illumination system in which "the excitation optics [1200] transform the beam to a line capable of exciting a row of the sample simultaneously", Trulson, for producing the line, suggests devices to homogenize excitation light from an array of LEDs. The emissions are imaged onto an array of light detectors and subsequent image lines are acquired by translating the sample relative to the optics head, col. 26, line 31-34.

Claim 3 (see also claims 1, 52 and 53)

Claim 3 was rejected over Rava in view of Trulson as applied to claim 1 and in further view of Mirzabekov et al (5,851,772). Mirzabekov does not make up for the numerous deficiencies of Rava or Trulson with respect to claim 1 or claim 3 9or newly added claim 52):

(1) Mirzabekov obviously requires movement of the chip relative to the microscope to view their area of interest since their chip of 1 cm x 1 cm may contain tens of thousands of elements, see col. 8, line 61-62, while using a 3x objective, it is only able to "project 2.7 x 2.7 mm of the microchip on the CCD", col. 10, lines 47-50.

(2) Mirzabekov has no suggestion to use virtually no magnification, i.e. limit to the range of about 25% down to reduction of the image 75%, claim 1, and achieve the sensing of a complete two dimensional array of interest in one frame, claim 1.

(3) Mirzabekov employs a mercury lamp to illuminate an object field, col. 10, line 45-49, having no suggestion of a diode lighting system that illuminates an entire two-dimensional array for simultaneous sensing in one frame (see also claim 8). The mere suggestion of Mirzabekov of a numerical aperture of a value also employed according to the present invention, taken with the other references relied on by the Examiner, fails to suggest the novel combination of the claims, or the result achieved.

Claim 6

Amended claim 6 requires the illumination system of the at least one light-emitting diode, to provide excitation illumination over the entire two-dimensional array on the substrate of a power density greater than 30 mW/cm^2.

Neither Rava, Trulson nor Mirzabekov teaches diode illumination of an entire two-dimensional array, let alone doing it at the significant claimed intensity with the claimed diode lighting system as a way to achieve a practical, inexpensive clinical reader, for which reason claim 6 is submitted to be unobvious over the cited references.

Claim 11

Claim 11 calls for the array reader of claim 1 constructed and arranged to deliver to the solid state sensor array an image of the field of view reduced between about 30% and 50%. Claim 11 was rejected on Rava in view of Trulson, relying on Trulson's statement beginning at column 27, line 7 that "In addition, resolution of the image may be manipulated by increasing or decreasing the magnification of the collection optics". This truism is certainly no direction to a person of ordinary skill to eliminate magnification entirely, and to adopt the claimed combination of reduction of the image between about 30% and 50%. The Examiner's suggestion of routine experiment must fail because there is no suggestion of Applicant's goal toward which to experiment, and certainly no suggestion to experiment in the direction of no positive

magnification (claim 11 is limited only to reduction in image size). Accordingly, it is submitted that claim 11 is patentable over the prior art cited in its rejection.

Claim 22

Claim 22 calls for the array reader of claim 1 in which the illumination system comprises at least two different light source sub-systems respectively of substantially different wavelengths, each comprised of at least one diode, each associated with a respective optical system delivering light along a path, the paths of the sub-systems to the substrate lying along respectively different axes, the axes being spaced apart about the substrate. Claim 22 was rejected as unpatentable over Rava in view of Trulson, and in further view of Walton (6,294,327). Walton is directed to a "...scanner instrument...using a novel light scattering and reflection technique ...", see col. 2 lines 51-54 and see Figure 6, "linear translation stage". While Walton does teach employing more than one light source, it is not for the purpose of exciting fluorophores or the like, and certainly not for imaging stimulated emission over an entire two-dimensional array in a single frame. Along with Rava and Trulson, Walton does not teach the combination of claim 1, let alone the combination of claims 1 and 22.

The other references

The other references relied upon by the Examiner (Mills, Giaever and Vo-Dinh only relate to chip features, not readers, and do not make up for the deficiencies of the principal references discussed above.

Claim 39 and 45

Method claims 39 and 45 have been amended to require that the respective methods employ the array reader of claim 1, and are submitted now to fall within elected Group I and be appropriate for examination in the present application. They are novel in employing the novel structure of claim 1 as well as in their own right. See also new method claim 56.

Claim 51

New Claim 51 has been added as follows: "51. The array reader of claim 1 in which the image collection and recording system has a field of view on the substrate of area between about 50 mm^2 and 300 mm^2." It corresponds to claim 4 of the original PCT application upon which the present application is based. The claim is considered to be pointedly useful in emphasizing the large field of view of this diode-illuminated, inexpensive array reader. Note how vastly larger this field is, compared to the Mirzabekov 2.7 mm x 2.7 mm field (area less than 8 mm^2), substantially a difference by an order of magnitude in area covered.

New Claims 53 to 56

New claims 53 , 54, 55 and 56 have been added as follows: 53. The array reader of claim 1 in combination with a carrier for the array comprising a substrate layer carried by a support body, said image collection and recording system residing on the same side of the substrate as does the array of features such that the path of illumination from the illumination system reaches the array before reaching the support body, the carrier beneath the substrate layer being opaque; 54. The array reader of claim 53 in which a main portion of the support body is transparent while an opaque coating is carried by the support body between the main portion of the support body and the substrate layer; 55. The array reader of claim 53 in which the substrate layer is ultrathin; and 56. A method of employing the array reader of claim 53 for reading an array.

The opaque carrier of these claims has the virtue of preventing light from regions beyond the substrate layer from reaching the detector, despite the large depth of field of the image collection and recording system that inherently accompanies its intermediate numerical aperture. See for example the specification, page 15 lines 5-9 and original PCT claims 14-16. This effect is further enhanced by an ultrathin nature of the substrate layer, see specification, page 14, line 28-page 15, line 4. The claimed combination and method enable low signal-to-noise ratio detection despite the use of the relatively inexpensive-to-produce intermediate numerical aperture (as opposed to the relatively high cost of a small numerical aperture inherent with confocal imaging systems of the main references).

Conclusion

For the reasons given all claims are submitted to be allowable over the cited references and early favorable action is solicited.

No fee is believed to be due. If, however, there are any charges or credits, please apply them to Deposit Account No. 06-1050, referencing Attorney Docket No. 13165-0005US1.

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Respectfully submitted,

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